PART 1 (COUNCIL DECISION 2002/813/EC)

SUMMARY NOTIFICATION INFORMATION FORMAT FOR THE RELEASE OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

In order to tick one or several possibilities, please use crosses (meaning x or X) into the space provided as (.)

A. General information

1. Details of notification

Application for authorization to use the genetically modified ide-cel (also known as BMS-986395 and bb2121) in Norway

(a) Member State of notification
(b) Notification number
(c) Date of acknowledgement of notification
(d) Title of the project
A Randomized, Open-Label, Phase 3 Trial to Compare the Efficacy and Safety of Idecabtagene Vicleucel with Lenalidomide Maintenance Versus Lenalidomide Maintenance Therapy Alone in Adult Participants with Newly Diagnosed Multiple Myeloma Who Have Suboptimal Response After Autologous Stem Cell Transplantation (KarMMa-9)
(e) Proposed period of release From 27-July-2023 until end 2031.

2. Notifier

Name of institution or company:
The sponsor of the study is Celgene Corporation, 86 Morris Avenue, Summit, New Jersey 07901, United States of America (USA). The notifier/applicant is Bristol Myers Squibb AB, P.O. Box 1172, 171 23 Solna, Sweden.

3. GMO characterisation

(a) Indicate whether the GMO is a:

viroid (.)
RNA virus (.)
DNA virus (.)
bacterium (.)
fungus (.)
animal
- mammals (X) Genetically modified human autologous T lymphocytes
- insect (.)
- fish (.)
- other animal (.) specify phylum, class

other, specify (kingdom, phylum and class)

(b) Identity of the GMO (genus and species)

The GMO, known as ide-cel, is a genetically modified autologous *Homo sapiens* T cell immunotherapy product consisting of T cells transduced with a lentiviral vector (LVV), which encodes an anti-BCMA Chimeric Antigen Receptor (CAR) that recognizes B-cell Maturation Antigen (BCMA) on BCMA-expressing cancer cells.

(c) Genetic stability – according to Annex IIIa, II, A(10)

The anti-BCMA CAR transgene is introduced to the T cells via transduction with a third-generation replication incompetent self-inactivating (SIN) lentivirus. Because the viral vector is integrated into the host genome, the CAR sequences will be present as a stable, integral part of the patient's DNA in the transduced T cells. The lentiviral vector (LVV) is designed so it encodes only genes necessary for the expression of the CAR and lacks the required genes for HIV replication or pathogenicity.

4. Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?

   Yes (X) No (.)

   If yes, insert the country code(s) ; AT, BE, CZ, DK, DE, FR, GR; IT; PL; ES, RO

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?

   Yes (X) No (.)

   If yes:

   - Member State of notification: BE
   - Notification number: LNE/AMV/HB/PB/CL/vr AMV/SBB219.2017 /0768R (Renewal Ref N°LNE/AMV/HB/PB/CL/vr AMV/SBB219.2019/1023); LNE/ AMV /HB/PB/CL/vr AMV /SBB219.2018/1016R

   - Member State of notification: FR
   - Notification number: DUO no. TG 4004, TG 4329, TG 3754, TG 3788, TG 6500, DUO no. 5549, DUO no. 5622, DUO no. 5547, DUO no. 5403

   - Member State of notification: DE
   - Notification number: CTA approval references 3269/02 (for study bb2121-MM-001 - EudraCT 2017-002245-29), 3525/01 (for study bb2121-MM-002 - EudraCT 2018-000264-28), 3525/14 (for study bb2121-MM-003 - EudraCT 2018-001023-38)

   - Member State of notification: IT
   - Notification number: BO/IC/Op2/18/002, BG/IC/Op2/18/001, BO/IC/Op2/18/003, BO/IC/Op2/19/004, TO/IC/Op2/19/011

   - Member State of notification: NL
   - Notification number: IM- MV 19-005_000.bes.1

   - Member State of notification: ES
   - Notification number: B/ES/17/18, B/ES/18/26, B/ES/18/30, B/ES/20/20

   - Member State of notification: SE

- Notification number: bb2121-MM-003 (EudraCT 2018-001023-38)

Please use the following country codes:
Austria AT; Belgium BE; Germany DE; Denmark DK; Spain ES; Finland FI; France FR; United Kingdom GB; Greece GR; Ireland IE; Iceland IS; Italy IT; Luxembourg LU; Netherlands NL; Norway NO; Portugal PT; Sweden SE

6. Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?

Yes (X) No (.)

If yes:

- Member State of notification: CA
- Notification number: Dossier ID: HC6-024-e205514, Control #: 211603; Dossier ID: HC6-024-e218933, Control #: 218933.

- Member State of notification: JP
- Notification number: not applicable

- Member State of notification: NO
- Notification number: 18/30232-11

- Member State of notification: UK
- Notification number: CHG:0046; 850: HM19/121856.

- Member State of notification: US
- Notification number: not applicable

7. Summary of the potential environmental impact of the release of the GMOs.

No environmental impact is expected from the administration of ide-cel drug product to subjects in clinical trial CA089-1043. Ide-cel drug product is supplied to the clinical site for infusion into the patient via intravenous route. Thus, the release of the transduced autologous T cells is limited to patient administration in a hospital setting and will not reach the environment at large. There are no mechanisms of dispersal outside the human body. Transduced cells are not viable in the environments outside of the patient. Viral persistence and replication in the environment are not possible due the use of a replication incompetent LVV.

B. Information relating to the recipient or parental organism from which the GMO is derived

1. Recipient or parental organism characterisation:

(a) Indicate whether the recipient or parental organism is a:

(select one only)

viroid (.)
RNA virus (.)
DNA virus (.)

bacterium (.)
fungus (.)
animal
- mammals (X) Autologous human T lymphocytes
- insect (.)
- fish (.)
- other animal (.)
(specify phylum, class)

other, specify

2. Name
(i) order and/or higher taxon (for animals): Primates
(ii) genus: *Homo*
(iii) species: *H. sapiens*
(iv) subspecies: Not Applicable
(v) strain: Not Applicable
(vi) pathovar (biotype, ecotype, race, etc.): Not Applicable
(vii) common name: Human

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:
Yes (X) No (.) Not known (.)

(b) Indigenous to, or otherwise established in, other EC countries:
(i) Yes (.) Questions 3b-3d are not applicable for humans cells

If yes, indicate the type of ecosystem in which it is found:

Atlantic ..
Mediteranean ..
Boreal ..
Alpine ..
Continental ..
Micronesial ..

(ii) No (.)
(iii) Not known (.)

(c) Is it frequently used in the country where the notification is made?
Yes (.) No (.) Not applicable to human cells

(d) Is it frequently kept in the country where the notification is made?
Yes (.) No (.) Not applicable to humans cells

4. Natural habitat of the organism

(a) If the organism is a microorganism

water	(.)
soil, free-living	(.)
soil in association with plant-root systems	(.)
in association with plant leaf/stem systems	(.)
other, specify	Not applicable to human cells

(b) If the organism is an animal: natural habitat or usual agroecosystem:
This is not applicable as ide-cel is a human T cell population intended for autologous use. The peripheral blood mononuclear cell (PBMC) starting material is obtained via apheresis from the patient, followed by ide-cel manufacture and infusion into the same patient.

5. (a) Detection techniques
Quantitative PCR and common techniques of blood cell analysis (e.g. flow cytometry).

(b) Identification techniques
Quantitative PCR and common techniques of blood cell analysis (e.g. flow cytometry).

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?
Yes (.) No (X) Human T cells are not classified under existing Community rules.

If yes, specify
…

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (.) No (X) Not known (.)

If yes:

(a) to which of the following organisms:

humans	(.)
animals	(.)
plants	()
other	(.)

(b) give the relevant information specified under Annex III A, point II. give the relevant information specified under Annex III A, point II. (A)(11)(d) of Directive 2001/18/EC

The GMO is derived from autologous T cells isolated from the peripheral blood of newly diagnosed patients with Multiple Myeloma who have suboptimal response after autologous stem cell transplantation (ASCT). The T cells cannot survive outside of the patient. The cells are not pathogenic and cannot persist or replicate in the environment or other organisms.

Patients are tested for HIV, HBV and HCV during screening (prior to blood donation) and excluded from the clinical trial if tested positive for or have a history of HIV infection, or if the results of the tests support an active HBV and HCV infection (Note: participants with a negative hepatitis B polymerase chain reaction assay or a negative hepatitis C virus RNA assay for viral load quantification for hepatitis B or C are permitted). Participants positive for hepatitis B surface antigen and/or anti-hepatitis B core antibody with a negative viral load are eligible and should be considered for prophylactic antiviral therapy. Participants with a prior history of active or chronic hepatitis C with a negative viral load are eligible and should be considered for prophylactic antiviral therapy. In addition, participants with systemic and uncontrolled infections, without improvement despite appropriate antimicrobials or requiring intravenous (IV) antimicrobials for management at screening, are excluded from the study.

Autologous blood leukapheresis source material is controlled for viral adventitious agents as per country specific guidances. The testing for adventitious agents (including HIV, HBV, HCV, syphilis, and HTLV-1/2) is performed on blood samples that are pulled at the time of leukapheresis or within 7 days post donation. Sponsor will process cells except in cases where the patient fails clinical trial eligibility criteria as detailed in the clinical protocol.

8. Information concerning reproduction

This information is not applicable for genetically modified human T lymphocytes in the recipient.

(a) Generation time in natural ecosystems:

(b) Generation time in the ecosystem where the release will take place:

(c) Way of reproduction: Sexual .. Asexual ..

(d) Factors affecting reproduction:

9. Survivability

This is not applicable as human T lymphocytes cannot survive in the environment.

(a) ability to form structures enhancing survival or dormancy:

(i)	endospores	(.)
(ii)	cysts	(.)
(iii)	sclerotia	(.)
(iv)	asexual spores (fungi)	(.)
(v)	sexual spores (funghi)	(.)
(vi)	eggs	(.)
(vii)	pupae	(.)
(viii)	larvae	(.)
(ix)	other, specify	

(b) relevant factors affecting survivability:

Human T cells require complex solutions, environmental, and physical controls, such as special media, temperature and CO_2, in order to survive outside the human body. Since these controls are not present in the general environment, the T cells will not survive in the general environment.

10. (a) Ways of dissemination

Human T cells are only transmitted between individuals through infusion or injection. There are no mechanisms of dissemination outside the human body; therefore, no dissemination in the environment is expected.

(b) Factors affecting dissemination

Should the human T cells be infused or injected into any human recipients other than the autologous patient, an immune cell-mediated response will rapidly eliminate the cells.

11. Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)

Reference is made to notification numbers provided in answer to question A.5 of this form.

C. **Information relating to the genetic modification**

1. Type of the genetic modification

(i)	insertion of genetic material	(X)
(ii)	deletion of genetic material	(.)
(iii)	base substitution	(.)
(iv)	cell fusion	(.)
(v)	others, specify	

2. Intended outcome of the genetic modification

Autologous humans T cells transduced ex vivo with the anti-BCMA02 CAR LVV leads to the integration of BCMA-specific CAR transgene into the host genome, resulting in the expression of the anti-BCMA02 CAR on the T cell surface. Ide-cel CAR T cells are effectively redirected toward recognition and lysis of BCMA-expressing cells, including malignant cells.

3. (a) Has a vector been used in the process of modification?

Yes (X) No (.)

If no, go straight to question 5.

(b) If yes, is the vector wholly or partially present in the modified organism?

Yes (X) No (.)

If no, go straight to question 5.

4. If the answer to 3(b) is yes, supply the following information

(a) Type of vector

plasmid	(.)
bacteriophage	(.)
virus	(X)
cosmid	(.)
transposable element	(.)
other, specify	

(b) Identity of the vector

The vector is a third-generation replication incompetent, self-inactivating (SIN) lentiviral vector derived from human immunodeficiency virus type 1 (HIV-1) encoding a CAR specific for BCMA.

(c) Host range of the vector

Lentiviral vectors of this type are capable of transducing animal and insect cells. However, it is important to emphasize that the Anti-BCMA02 CAR LVV is not replication competent and does not encode any pathogenic genes.

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype

Yes (X) No (.)

antibiotic resistance (.)

other, specify:

The therapeutic gene product (anti-BCMA T cell receptor) is identified by flow cytometry, and lentiviral vector back-bone sequences are identified and quantified by qPCR.

Indication of which antibiotic resistance gene is inserted:

This is not applicable as no antibiotic resistance genes are present in the anti-BCMA CAR LVV. Plasmids used in the suspension based LVV manufacturing process uses an antibiotic-free selection system and are referred to as antibiotic free (AF) plasmids. The AF plasmids were prepared from the set of plasmids that contain the ampicillin resistance gene. Standard molecular biology techniques were used to replace the plasmid backbone ampicillin resistance gene with RNA-out anti-sense RNA (antibiotic free). No other manipulation of plasmid structural elements was performed.

(e) Constituent fragments of the vector

Anti-BCMA02 CAR LVV is enveloped by a lipid membrane derived from the outer lipid bilayer of HEK293T cells. Embedded in this membrane is the vesicular stomatitis virus glycoprotein G (VSV-G) pseudotyping envelope protein. Gag, the most abundant protein in the virion, is cleaved during maturation into three individual structural proteins, the capsid, matrix, and nucleocapsid, that form layers underneath the lipid membrane. The matrix forms the outer layer that surrounds the viral core. The core is delimited by a capsid protein (p24) shell that encloses the nucleoprotein complex; this complex contains two identical strands (dimer) of the RNA genome complexed with nucleocapsid proteins. Anti- BCMA02 CAR LVV particles contain 3 viral enzymes encoded by Pol: reverse transcriptase, integrase, and protease.

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(f) Method for introducing the vector into the recipient organism

(i)	transformation	(.)
(ii)	electroporation	(.)
(iii)	macroinjection	(.)
(iv)	microinjection	(.)
(v)	infection	(.)
(vi)	other, specify	Transduction

5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?

Not applicable.

(i)	transformation	(.)
(ii)	microinjection	(.)
(iii)	microencapsulation	(.)
(iv)	macroinjection	(.)
(v)	other, specify	(.)

6. Composition of the insert

(a) Composition of the insert
Summarized in 6(c).

(b) Source of each constituent part of the insert
Summarized in 6(c).

(c) Intended function of each constituent part of the insert in the GMO
Insert Component: HIV-1 Repeat, unique 5'site PBS and Ψ packaging sequences
Source: pNL4-3; GenBank Reference Accession #M19921.2 (Maldarelli et al., 1991)
Function: Required for insertion of provirus DNA into the chromosome

Insert Component: HIV-1 gag region
Source: pNL4-3 GenBank Reference Accession #M19921.2 (Maldarelli et al., 1991)
Function: Secondary structures required for vector packaging

Insert Component: HIV-1 Central Polypurine Tract (cPPT)
Source: pNL4-3 GenBank Reference Accession #M19921.2 (Maldarelli et al., 1991)
Function: Required for reverse transcription

Insert Component: HIV-1 env region Rev Response Element (RRE)
Source: PgTAT-CMV GenBank Reference Accession #M14100.1 (Malim et al, 1988)
Function: Binding site for Rev, for efficient packaging of the vector RNA

Insert Component: MND promoter
Source: pccl-c-MNDU3c-x2 (Challita et al., 1995)
Function: Drives T cell-specific expression

Insert Component: Anti-BCMA02 scFv (VL-linker-VH)

Source: Synthetic
Function: Recognizes BCMA antigen on tumor cells

Insert Component: CD8a hinge and Transmembrane region
Source: GenBank Reference Accession # NM_001768 (Milone et al., 2009)
Function: Ensures correct T cell receptor conformation

Insert Component: CD137 (4-1BB) signaling domain
Source: GenBank Reference Accession # NM_001561 (Milone et al., 2009)
Function: Ensures correct T cell receptor function

Insert Component: CD3-ζ signaling domain
Source: GenBank Reference Accession # NM_000734 (Milone et al., 2009)
Function: Ensures correct T cell receptor function

Insert Component: HIV-1 unique 3' region and repeat region.
Source: pNL4-3; GenBank Reference Accession #M19921.2 (Maldarelli et al., 1991)
Function: Required for insertion of provirus DNA into the chromosome

(d) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome (X)
- other, specify

(e) Does the insert contain parts whose product or function are not known?
Yes (.) No (X)
If yes, specify

D. Information on the organism(s) from which the insert is derived

1. Indicate whether it is a:

viroid (.)
RNA virus (X)
DNA virus (.)
bacterium (.)
fungus (.)
animal
- mammals (X)
- insect (.)
- fish (.)
- other animal (.)
(specify phylum, class)

other, specify

2. Complete name

This section is not applicable. The anti-BCMA02 CAR LVV is a viral vector construct containing the gene of interest. This vector uses the myeloproliferative sarcoma virus enhancer, negative control

region deleted, dl587rev primer-binding site substituted (MND) promoter to drive expression of the chimeric receptor. The anti-BCMA CAR is a multi-domain protein consisting of the extracellular single chain variable fragment (scFv), the CD8α hinge domain, a transmembrane domain (CD8 TM), the intracellular CD137 co-stimulatory (4-1BB) and CD3ζ chain signaling domains. The Anti-BCMA02 CAR LVV does not encode for any HIV proteins; the only HIV-derived sequences in the transcript are the repeat regions that have been made SIN by deleting promoter/enhancer sequences, and attenuated regions of the proteins and elements that aid in the production, packaging, or transfer of the transcript containing the therapeutic gene.

(i)	order and/or higher taxon (for animals)	…
(ii)	family name for plants	…
(iii)	genus	Lentivirus; Human
(iv)	species	HIV; Human
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	…

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?

Yes (.) No (X) Not known (.)

If yes, specify the following:

(b) to which of the following organisms:

humans (.)
animals (.)
plants (.)
other ..

(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism

Yes (.) No (X) Not known (.)

If yes, give the relevant information under Annex III A, point II(A)(11)(d):
Not applicable.

4. Is the donor organism classified under existing Community rules relating to the protection of human health and the environment, such as Directive 90/679/EEC on the protection of workers from risks to exposure to biological agents at work?

Yes (X) No (.)

If yes, specify: Wild type HIV is classified as a Group 3 organism; however, the third generation, replication-incompetent SIN lentivirus used for transduction of T cells is not pathogenic anymore as no infectious viral particles can be produced after transduction and is classified as Group 2. All pathogenic and replicative properties of the HIV virus are removed, preserving only their gene transporting capabilities.

5. Do the donor and recipient organism exchange genetic material naturally?
Yes (.) No (X) Not known (.)

E. Information relating to the genetically modified organism

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

(a) is the GMO different from the recipient as far as survivability is concerned?
Yes (.) No (X) Not known (.)
Specify

(b) is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?
Yes (.) No (X) Unknown (.)
Specify

(c) is the GMO in any way different from the recipient as far as dissemination is concerned?
Yes (.) No (X) Not known (.)
Specify

(d) is the GMO in any way different from the recipient as far as pathogenicity is concerned?
Yes (.) No (X) Not known (.)
Specify

2. Genetic stability of the genetically modified organism

The sequences encoding the BCMA-specific CAR are introduced to the human T cells *via* transduction with a replication-incompetent self-inactivating lentiviral vector. Due to integration of the viral vector into the host genome, the CAR sequences will be present as a stable, integral part of the host DNA in transduced cells during the duration that the cells persist following infusion. The inserted CAR transgene encodes only genes necessary for the expression of the BCMA-specific CAR and lacks the required genes for HIV replication or pathogenicity.

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?
Yes (.) No (X) Unknown (.)

(a) to which of the following organisms?

Not applicable.

humans (.)
animals (.)

plants (.)
other (.)

(b) give the relevant information specified under Annex III A, point II(A)(11)(d) and II(C)(2)(i)
The GMO is neither pathogenic nor harmful. No safety issues have been reported during the nonclinical and clinical development of ide-cel.

Moreover, the LVV used to transduce the autologous T lymphocytes, is a replication-incompetent self-inactivating lentiviral vector. It is not capable of replicating in human cells and therefore cannot form progeny virions that would result in the spread of a replicating virus or increase probability of recombination with other retroviruses. The LVV uses a split-genome third-generation system where the plasmids encoding the segments and genes required to form the viral vector are segregated onto three separate helper plasmids: the envelope glycoprotein (not derived from a lentivirus) is on one plasmid, the *gag* and *pol* genes on another plasmid (derived from HIV-1), and the *rev* gene on a third plasmid (derived from HIV-1). The transgene is encoded on a transfer plasmid (derived from HIV-1 but self-inactivating due to a deletion in the 3'LTR). All sequences are provided *in trans* via transfection of plasmids into the HEK-293T cell line which only allows for transient expression of these constructs during the viral vector production stage. The risk for RCL is even further reduced by retaining the Rev-dependence of the viral vector. Rev is required for export of the RNA genome transgene from the nucleus into the cytoplasm for protein expression and packaging. Since Rev is provided only *in trans* and since the Rev protein is not packaged in the virus the chance that a lentiviral RNA genome can continue its nuclear export in transduced cells is highly unlikely. Finally, the self-inactivating nature of the vector means that expression of the LTR is significantly reduced due to the 3'LTR deletion and the absence of the HIV-1 *tat* gene (normally required for LTR-driven transcription).

Based on the conditions and wash steps of the manufacturing process, it is expected that no residual infectious lentiviral vector particles will be present in the ide-cel drug product.

Finally, the T cells cannot survive outside of the patient. The cells are not pathogenic and cannot persist or replicate in the environment or other organisms. Patients are tested for HIV during screening and excluded from the clinical trial if tested positive, thus eliminating risk of recombination with any remaining LVV in the drug product.

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
Cells transduced with the anti-BCMA02 CAR LVV (ide-cel drug product) are not released into the environment and are not stable under uncontrolled environmental conditions. Following administration of the product, patients are monitored for persistence of ide-cel using qPCR specific to the integrated LVV sequences.

(b) Techniques used to identify the GMO

Quantitative PCR is used to measure the integrated vector sequences and detect the presence of transduced T cells. Flow cytometry is used to confirm expression and identify cells expressing the BCMA-specific CAR.

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)

The ide-cel drug product (T cells transduced with anti-BMCA CAR LVV) is not released into the environment. It will be administered intravenously into subjects enrolled in ide-cel clinical studies for the treatment of multiple myeloma, under highly controlled conditions for cell transplant at the clinical study site. The transduced cells may migrate to the bone marrow or may remain in the peripheral circulatory system post-infusion.

The ide-cel drug product begins with the isolation of PBMCs at a cGMP manufacturing facility in the EU from the patient's leukapheresis collection, which is performed at the clinical study site. The PBMCs are transported to a cGMP manufacturing facility where they are transduced with the anti-BCMA02 CAR LVV to produce the final ide-cel drug product. Each lot of ide-cel drug product is tested to ensure identity and purity prior to quality release. The quality released ide-cel drug product is then transported to the clinical site under controlled conditions, where it is stored prior to infusion.

2. Is the site of the release different from the natural habitat or from the ecosystem in which the recipient or parental organism is regularly used, kept or found?

Yes (.) No (X)

If yes, specify

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):

Oslo University Hospital, Rikshospitalet, Department of Hematology
Postal address: Postboks 4950 Nydalen, 0424 Oslo.
Visiting address: Sognsvannsveien 20, 0372 Oslo

(b) Size of the site (m^2):

(i) actual release site (m^2):

Not Applicable as administration of ide-cel to patient will take place in a hospital room

(ii) wider release site (m^2):

Not Applicable as administration of ide-cel to patient will take place in a hospital room

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:

Not applicable since the release will take place during a clinical study in investigational sites

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO

Not applicable since the release will take place during a clinical study in investigational sites

4. Method and amount of release

(a) Quantities of GMOs to be released:

The GMO is not intended to be released into the environment. Ide-cel will be infused once per patient at a target dose range of 300 to 460 x 10^6 CAR+ T cells.

(b) Duration of the operation:

The duration of the operation is 1 hour, which is the time it takes to infuse the patient with the drug product during the clinical trial.

(c) Methods and procedures to avoid and/or minimize the spread of the GMOs beyond the site of the release

The ide-cel drug product containing T cells transduced with the anti-BCMA02 CAR LVV is administered intravenously into the subject under standard controlled conditions for cell transplant at the clinical site. Ide-cel will be shipped to the clinical site in a validated shipping container prior to the scheduled administration to the patient. Storage of the product in the liquid nitrogen tanks of site is optional, according to country-specific requirements. Ide-cel will be thawed on site and administered to the patient via intravenous infusion in a hospital infusion area. The appropriate clinical site personnel will be trained in handling and administration, thawing and product accountability procedures. Any manipulations of the ide-cel drug product will be carried out under the appropriate biohazard containment level. Prior to and during administration the GMO is contained; there will be no activities where third parties including medical personnel can come into direct contact with it. The administration of ide-cel will be performed at specialized medical centers equipped for the safe administration of biological or cellular products, and by experienced health care professionals, appropriately trained in hygiene procedures and standards regarding safety and infectious materials handling. Ide-cel contains autologous human T cells and therefore, healthcare professionals should employ universal precautions for the prevention of transmission of blood-borne infections. Any partially used or unused ide-cel (material remaining in the bags), the bags, the absorbent barrier pads, any supplies used in the preparation and administration process, including the IV administration set, must be disposed of in accordance with the institution's biohazard disposal policy for tissues with bloodborne pathogens or potentially infectious patient material. Used transfusion bags and protective equipment will be collected in a sealable bag and placed in a dedicated and properly labelled container, which will then be delivered to the waste room of the GMP facility. Contaminated waste and materials will be autoclaved. Other than standard cleaning and sanitation of the hospital room and the disposal of product waste and contaminated materials, no particular treatment of the site is necessary. Human T cells require complex solutions, environmental, and physical controls to survive outside the human body. Without these controls in the general environment the T cells will not survive.

5. Short description of average environmental conditions (weather, temperature, etc.)
Ide-cel will be administered in a clinical setting at room temperature.

6. Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human health impacts from the release.
Abecma® is approved in the EU and there is no adverse environmental or human health impact since its launch. There are no applicable relevant data regarding potential environmental impacts from previous releases carried out with ide-cel. Ide-cel cannot persist in the environment.

G. Interactions of the GMO with the environment and potential impact on the environment, if significantly different from the recipient or parent organism

This section is not applicable. The target organism is the autologous patient recipient. The transduced autologous T cells are not released into the environment.

1. Name of target organism (if applicable)

(i)	order and/or higher taxon (for animals)	*Homo sapiens* (Primates)
(ii)	family name for plants	…
(iii)	genus	...
(iv)	species	...
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	…

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)

Ide-cel drug product contains autologous T cells transduced with the anti-BCMA02 CAR LVV. Ide-cel is used in the treatment of patients with multiple myeloma. After infusion, the ide-cel CAR T cells will target and bind to BCMA+ cells resulting in the lysis of the BCMA-expressing cells. Transduced cells are not viable in the environment outside of the subject.

3. Any other potentially significant interactions with other organisms in the environment.

None expected. Possible interaction with other foreign organisms, such as HIV (and that could lead to in vivo recombination leading to formation of RCL), is extremely low. Subjects are screened for HIV prior to acceptance into the current ide-cel clinical study. No ide-cel drug product is made from HIV positive subjects, therefore eliminating the possibility of recombination of the LVV with HIV. The transduced cells are not viable outside of the body of the treated patients. No shedding of the LVV used to manufacture ide-cel has been reported. The administration of the GMO product to immunocompetent people leads to rejection of the GMO cells. In summary, no interactions are expected between ide-cel and other organisms in the environment.

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?

Yes (.) No (X) Not known (.)

Give details

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established

There is no possibility to disseminate ide-cel from the clinical study site to any other ecosystem. All clinical waste is destroyed according to hospital's procedures for the disposal of bio-hazardous waste.

6. Complete name of non-target organisms which (taking into account the nature of the receiving environment) may be unintentionally significantly harmed by the release of the GMO

There are no non-target organisms which may be unintentionally significantly harmed by the release of the GMO. This section is not applicable.

(i) order and/or higher taxon (for animals) …
(ii) family name for plants …
(iii) genus …
(iv) species …
(v) subspecies …
(vi) strain …
(vii) cultivar/breeding line …
(viii) pathovar …
(ix) common name …

7. Likelihood of genetic exchange in vivo

(a) from the GMO to other organisms in the release ecosystem:

The ide-cel drug product is made with a replication incompetent vector that stably inserts the proviral DNA encoding the CAR into the genome of the autologous T cells. The anti-BCMA02 CAR transgene is not capable of mobilization or amplification. Therefore, gene transfer to unintended organisms is not anticipated and is extremely low for the following reasons:

1) Potential risks to the treated subject include the theoretical risk of generation of a replication competent lentivirus (RCL). However, it is important to note that all viral genes responsible for HIV pathogenicity and replication have been removed from the proviral sequence, and replaced with a human therapeutic gene, thereby making the risk of RCL formation negligible. No new viral particles can be assembled and shed from the final host cell due to the absence of all the accessory proteins that confer infectivity and replicative potential to the lentivirus in this proviral form.

2) Subjects are screened for HIV prior to acceptance into the current ide-cel clinical study. No ide-cel product is made from HIV positive subjects, therefore eliminating the possibility of recombination of the inserted proviral sequences with HIV.

(b) from other organisms to the GMO:

The ide-cel drug product will exist as differentiated T cells in the patient. While it is always possible that human subjects are infected with other organisms, there is no added risk to the subject as the GMO does not encode any viral or pathogenic genes.

(c) likely consequences of gene transfer:

Once ide-cel drug product is created, no further gene transfer is anticipated.

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g. microcosms, etc.):

This is not applicable. No studies of the behavior and characteristics of the GMO and its ecological impact carried out in stimulated natural environments were performed.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)

This is not applicable.

H. Information relating to monitoring

1. Methods for monitoring the GMOs

Upon infusion into the subject, CAR-positive T cells will be detected using cytometric methods for identification and quantification of the therapeutic cell type, with a labeled antibody specific to the anti-BCMA CAR.

Ide-cel is administered as a single course of treatment, subjects are followed on study for safety and efficacy evaluations for approximately 5 years after the last patient has been randomized. In addition, because this protocol involves gene transfer, follow-up for long-term toxicity, retroviral vector safety, and survival status will continue to be monitored under a separate LTFU protocol (GC-LTFU-001) for up to 15 years after ide-cel infusion as per health authority guidelines.

In the long term follow up, subjects will undergo a routine (at least semi-annual or annual) physical examination and medical history, including concomitant medications and adverse events (AEs), with particular attention paid to features possibly related to retrovirus-associated events such as new malignancies, as well as new incidence or exacerbation of a pre-existing neurologic disorder, new incidence or exacerbation of a prior rheumatologic or autoimmune disorder, new incidence of hematologic disorders, or new infections. In addition, laboratory studies will be performed to evaluate routine safety endpoints, ide-cel vector persistence, and RCL.

2. Methods for monitoring ecosystem effects

This is not applicable as the ide-cel drug product is not released into the environment nor capable of surviving in the environment.

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms

This is not applicable as ide-cel is not released into the environment and no genetic material is expected to be donated to other organisms other than the patient for whom the ide-cel drug product has been specifically manufactured. Moreover, the administration of the GMO product to immunocompetent human subject who is not the autologous patient leads to an immune-mediated rejection of the GMO cells.

4. Size of the monitoring area (m^2)

This is not applicable as the ide-cel drug product is not released into the environment nor capable of surviving in the environment.

5. Duration of the monitoring

See response to H. 1

6. Frequency of the monitoring

See response to H. 1

I. Information on post-release and waste treatment

1. Post-release treatment of the site
Celgene will provide a ide-cel Product Administration Manual to all participating sites; all product handling should be carried out as per the Product Administration Manual. Any product waste and potentially contaminated materials after administration must be disposed as outlined in the Product Administration Manual per the institution's biohazard disposal safety measures in place for bloodborne pathogens or potentially infectious patient material. This destruction will be clearly documented and kept available in the records. These procedures and containment measure will ensure safe handling and prevention of any release into the environment.

2. Post-release treatment of the GMOs
No post-release treatment of the GMO applies, other than the disposal of product waste and contaminated materials as described under I.1. Human T cells require complex solutions, environmental, and physical controls in order to survive outside the human body. Without these controls in the general environment the T cells will not survive.

3. (a) Type and amount of waste generated
Any partially unused product (remaining in the product container(s)) and materials used for the administration of ide-cel, including product container(s), IV administration sets, and any supplies used in the preparation that have been in contact with ide-cel.

3. (b) Treatment of waste
Any product waste and potentially contaminated materials after administration must be disposed as outlined in the Product Administration Manual per the institution's biohazard disposal safety measures in place for bloodborne pathogens or potentially infectious patient material. This destruction will be clearly documented and kept available in the records.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread
Standard policies and procedures are in place at hospitals and research institutions for the treatment of medical waste which may contain bloodborne pathogens. Ide-cel (drug product) is not viable in the environment outside of the body of the treated patient. It is not possible for the drug product to spread into the environment. The anti-BCMA CAR lentiviral vector is

used to transduce ex vivo the autologous T cells in the controlled and insulated manufacturing laboratory setting based outside the EU. It degrades rapidly in the environment.

2. Methods for removal of the GMO(s) of the areas potentially affected
In case of accidental spill of ide-cel (drug product), decontamination is performed according to hospital spill procedures, such as wearing personal protective equipment, covering spill with absorbent, applying hospital approved disinfectant for appropriate contact time, and disposing of waste as biohazardous. The study team at site, which will be involved in the study drug product administration will be fully trained to the study requirements and to the hospital's procedures.

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread
No plant, animal or soil will be in the transplant unit where ide-cel is administered to the subject.

4. Plans for protecting human health and the environment in the event of an undesirable effect
The ide-cel drug product (transduced cells) and the anti-BMCA CAR lentiviral vector do not encode any pathogenic gene. The transduced cells are not viable outside of the body of the treated subjects. The lentiviral vector used to manufacture ide-cel degrades rapidly in the environment. The administration of the GMO product to immunocompetent people leads to rejection of the GMO cells. Therefore, no undesirable effects are expected.